FAST FACTS

NRG GU011: A PHASE II DOUBLE-BLINDED, PLACEBOCONTROLLED TRIAL OF PROSTATE OLIGOMETASTATIC RADIOTHERAPY WITH OR WITHOUT ANDROGEN DEPRIVATION THERAPY IN OLIGOMETASTATIC PROSTATE CANCER

ELIGIBILITY CRITERIA

1. Inclusion Criteria

1.1 Pathologically (histologically or cytologically) proven diagnosis of prostate adenocarcinoma at any anatomical location (for example, prostate, metastatic site), including intraductal or ductal carcinoma, at any time before registration.

1.2 Age ≥ 18 years.

1.3 ECOG Performance Status 0-2 within 180 days prior to registration

1.4 Prior curative-intent treatment to the prostate, by either:

- External beam and/or brachytherapy to: Prostate alone, prostate and seminal vesicles, prostate and pelvic nodes, or radiation to all three sites.
- Radical prostatectomy alone, radical prostatectomy plus postoperative radiotherapy to the prostate bed, or radical prostatectomy plus postoperative radiotherapy to the pelvic nodes.

1.5 Must meet study entry criteria based on the following diagnostic workup within 180 days prior to registration:

- History and physical examination;
- Fluciclovine or PSMA PET scan (Must be positive with exception of local disease); PET must be combined with either CT or MRI, but a diagnostic CT or MRI reading/interpretation is not required.

1.6 1 - 5 oligometastatic lesions in bone and/or nodal/soft tissue sites on fluciclovine or PSMA PET within 180 days prior to registration and includes at least ONE of the following:

- Bone – each metastasis is counted (for example, 2 distinct lesions in the right ilium count as 2 oligometastatic lesions),
- Extrapelvic Nodal/ soft tissue – requires at least one extrapelvic inguinal or a nodal/soft tissue lesion superior to the iliac bifurcation (that is, AJCC M1a version 8). Note: Although a patient must have bone and/or extrapelvic disease to be eligible, when counting the number of oligometastatic lesions, each lymph node lesion, whether pelvic or extrapelvic, is counted (for example, 2 distinct lymph nodes in the right external iliac basin count as 2

oligometastatic lesions; one extrapelvic and one pelvic node count as 2 oligometastic lesions, etc).

1.7 Serum total prostate-specific antigen (PSA) <10.0 ng/mL that also meets ONE of the following PSA recurrence definitions:

- PSA > post-RT nadir PSA + 2 ng/mL obtained within 180 days prior to registration, if patient received-radiation therapy to intact prostate, or
- Current PSA > 0.2 ng/mL, with a second confirmatory PSA > 0.2 ng/mL if patient received a radical prostatectomy with or without post-op RT. The initial PSA may be outside 180 days BUT the second confirmatory PSA must be within 180 days prior to registration, or
- PSA > 0.2 ng/mL with at least two rises from treatment nadir with the most recent PSA within 180 days prior to registration, if patient received radiation therapy to intact prostate.

1.8 Must have > 3 PSA values within the last two years since end of primary treatment or within the last 2 years prior to registration, whichever is less. *Note: PSA doubling time must be calculated by entering all PSA values since end of primary treatment or within the last 2 years prior to registration (whichever is less) into the PSA Doubling Time Calculator found at MDCalc.com (https://www.mdcalc.com/psadoubling-time-psadt-calculator).*

1.9 Serum total testosterone >100 ng/dL within 180 days prior to registration. Note: Prior androgen deprivation therapy (other than bilateral orchiectomy) is allowed if discontinued prior to registration and serum total testosterone is ≥100 ng/dL.

1.10 Adequate hepatic function within 180 days prior to registration defined as follows:

- Total Bilirubin: ≤ 1.5 × institutional upper limit of normal (ULN) (Note: In subjects with Gilbert's syndrome, if total bilirubin is >1.5 × ULN, subject is eligible if direct bilirubin is ≤1.5 × ULN), and
- AST(SGOT) and ALT(SGPT): ≤ 2.5 × institutional ULN

1.11 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

Note: Known positive test for hepatitis B virus surface antigen (HBV sAg) indicating acute or chronic infection would make the patient ineligible unless the viral load becomes undetectable on suppressive therapy. Patients who are immune to hepatitis B (anti-Hepatitis B surface antibody positive) are eligible (e.g. patients immunized against hepatitis B).

1.12 2 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

Note: Known positive test for hepatitis C virus ribonucleic acid (HCV RNA) indicating acute or chronic infection would make the patient ineligible unless the viral load becomes undetectable on suppressive therapy.

1.13 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

1.14 The patient must agree to use a highly effective contraception (even men with vasectomies) if he is having sex with a woman of childbearing potential or with a woman who is pregnant while on study drug and for 2 weeks following the last dose of study drug. Please see section 9.1.4 for more details.

1.15 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry and, for patients treated in the U.S., authorization permitting release of personal health information.

2.0 INELIGIBILITY CRITERIA

2.1 Clinical, biopsy-proven, or radiologic (conventional or PET imaging) evidence of local tumor recurrence in the prostate and/or periprostatic/seminal vesicle region after radiotherapy, or in the prostate bed after prostatectomy.

Note: if a patient had a prior local recurrence and received local salvage therapy, the patient is eligible if there is no current evidence of disease in the prostate/prostate bed. Patients with positive findings on examination or imaging remain eligible if biopsy of the site is negative for cancer. Patients who have a positive PET scan in the prostate or prostate bed and have undergone local therapy since PET but prior to enrollment to NRG-GU011 are eligible without a repeat PET scan

2.2 Currently on androgen deprivation or anti-androgen therapy.

2.3 Spinal cord compression, or spinal intramedullary, brain, and/or visceral (for example liver, lung, etc.) metastasis. Note: Spinal metastases (PET-detected) with epidural extension are eligible if there is >0.3cm spatial separation between the gross tumor volume and spinal cord.

2.4 Biopsy-proven prostatic carcinoma with signet-ring, sarcomatoid, or neuroendocrine features (for example, small cell).

2.5 Prior metastatic or non-metastatic, invasive malignancy (except non metastatic, non-melanomatous skin cancer) unless continuously disease free for > 3 years.

2.6 Prior chemotherapy for prostate cancer or bilateral orchiectomy. Note: Prior chemotherapy for a different cancer is allowed if continuously disease-free for > 3 years;

2.7 Prior radiotherapy to a lesion identified in 3.1.6 (i.e. oligometastatic recurrence by PET) Note: *Lesions outside of a previously irradiated planning treatment volume (PTV) are eligible as long as the prescription isovolume dose of any prior radiotherapy course is > 2.0cm distant from new lesion*

2.8 Inability to treat all oligometastatic sites with radiotherapy in the judgement of the investigator.

2.9 Intrapelvic lymph nodes as only site of prostate cancer recurrence

2.10 Inability to swallow whole, undivided, unchewed, and uncrushed pills

2.11 Known gastrointestinal disorder affecting oral medication absorption

2.12 Co-morbidity defined as follows:

- Patients with any comorbidities that would prohibit completion of protocol specified therapy.
- Inflammatory Bowel Disease in patients in whom abdominopelvic radiotherapy is planned
- History of congenital long QT syndrome;
- Current severe or unstable angina;
- New York Heart Association Functional Classification III/IV Heart Failure (Note: Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification.)